production and deleterious accumulation of **[an]** extracellular matrix **[component]** in a tissue comprising:

contacting the tissue with an **[agent]** anti-TGF-β antibody that binds to TGF-β;

whereby the binding of the **[agent]** anti-TGF-β antibody to the TGF-β suppresses the deleterious accumulation of the TGF-β-induced extracellular matrix **[component]** in the tissue.

25. (Amended) The method of claim **[24]** 21, wherein the condition is scarring.

**REMARKS**

By the present communication, claims 21 and 25 have been amended, and claim 24 has been canceled to expedite prosecution of the remaining claims. No new matter is introduced by the subject amendments as all amended claim language is fully supported by the specification.

The provisional rejection of claims 21-25 under the doctrine of obviousness-type double patenting over application Serial Nos. 07/803,285 and 07/467,888 is moot due to the abandonment of these applications. The provisional double-patenting rejection of claims 21-25 over application Serial No. 08/407,942, is held in abeyance at this time.

The rejection of claims 21-25 under 35 U.S.C. §112, first and second paragraphs, is respectfully traversed. It is respsectully submitted that the Examiner's concern with respect

to the term "agent" has been rendered moot by the amendments submitted herewith deleting such term.

Regarding the scope of pathologies enabled, the Examiner asserts, at p. 3, lns. 1-5 of Paper No. 52, that:

> [A]pplicants have addressed the issue of the animal model in relation to TGF-beta pathologies but the claims are not so limited to any disease in particular. Applicant's arguments are not commensurate with the scope of the claims.

Contrary to the Examiner's assertion regarding the scope of pathologies, it is respectfully submitted that the claims are not required to be limited to any diseases in particular.

Appplicants' invention, as defined by claim 21 as amended, is directed to:a method of decreasing the deleterious accumulation of extracellular matrix associated with a pathology or a condition characterized by the TGF-β-induced production and deleterious accumulation of extracellular matrix in a tissue comprising:

contacting the tissue with an anti-TGF-β antibody that binds to TGF-β;

whereby the binding of the anti-TGF-β antibody to the TGF-β suppresses the deleterious accumulation of the TGF-β-induced extracellular matrix in the tissue.

Regarding the scope of diseases enabled, Applicants' specification, at p. 9, ln. 6-13, teaches that:

> The pathologies capable of treatment are characterized by an accumulation of extracellular matrix and include glomerulonephritis, adult respiratory distress syndrome and cirrhosis of the liver. However, these pathologies are merely representative and a person skilled in the art would readily recognize the method to be useful in any pathology associated with accumulation of extracellular matrix.

It has long been settled that the requirements of 35 U.S.C. §112, first paragraph can be fulfilled by the use of illustrative examples or by broad terminology. In re Anderson, 176 USPQ 331, 333 (CCPA 1973):

> ...we do not regard section 112, first paragraph, as requiring a specific example of everything within the scope of a broad claim . . . What the Patent Office is here apparently attempting is to limit all claims to the specific examples, notwithstanding the clear disclosure of a broader invention. This it may not do.

Moreover, the Examiner has acknowledged in Paper No. 46, p. 5, ln. 17-19, that: "Applicant's arguments concerning manipulating the specific effect of TGF-[β] and that this has utility in controlling or the undesirable accumulation of ECM are persuasive..." In addition, the Examiner has previously acknowledged, in Paper No. 34, p. 10, ln. 19-24, that:

> It would have been obvious to apply the concept [of substituting the treatment of one disease for another] to diseases characterized by excess TGF-beta production and having increased ectracellular matrix production since the ability of the antibody to bind to TGF-beta is irrespective of tissue location or cell type, **lacking evidence to the contrary**. (emphasis added)

In addition, analgous to another of the Examiner's previous acknowledgments at the sentence bridging pgs. 10-11 of Paper No. 34, it is respectfully submitted that:

> it would have been obvious to one of ordinary skill to apply the treatment of [Applicants] to other diseases characterized by overproduction of extracellular matrix **and have a reasonable expectation of success** once the basis of the diseases had been recognized as being TGF-beta induced, **lacking evidence to the contrary.** (emphasis added)

In view of the Examiner's multiple acknowledgments, it is respectfully submitted that those of skill in the art would reasonably expect that Applicants' claimed method could be applied to the treatment of a variety of diseases characterized by TGF-β-induced deleterious accumulation of extracellular matrix.

Moreover, an assertion by the PTO that the enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubts expressed. In re Armbruster, 512 F2d 676, 185 USPQ 152 (CCPA 1975). It is respectfully submitted that the Examiner has provided no evidence or reasoning, that would contradict her own prior admissions set forth above, on which to base the requirement for limiting the claims to particular diseases. In this instance, it would not require undue experimentation to practice the invention as claimed.

In addition, Applicants respectfully submit that publications, "though dated after applicants' filing date, can be

used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification." In re Brana, 34 USPQ 2d 1436, 1441 n.19 (Fed. Cir. 1995)(citing In re Marzocchi, 169 USPQ at 370 n.4). Such publications go "to prove that the disclosure was in fact enabling when filed (i.e., demonstrated utility)." id.

Regarding the scope of pathologies enabled by Applicants' invention, TGF-β has clearly been implicated in the excess accumulation of extracellular matrix (ECM), resulting in dermal scarring, glomerulonephritis, and lung fibrosis, and like pathologies. In addition, the TGF-β inhibiting agent, anti-TGF-β antibody, has been found effective in treating proliferative mesangial glomerulonephritis (see Border et al., 1992, Kidney Intl. **41**:566-570, and the like). This disease is representative of a large group of diseases known as fibroproliferative diseases (reviewed in *Border and Ruoslahti*, J. Clin. Invest., 90:1 (1992) and *Border and Noble*, NEJM, 331:1286 (1994), which was previously submitted as Exhibit B in our previous Response mailed August 19, 1997). In these diseases, which include liver cirrhosis, lung fibrosis, intimal hyperplasia, atherosclerosis, rheumatoid arthritis and others, the mesenchymal component of the tissue expands and makes excessive extracellular matrix, obliterating the parenchymal tissue and thereby destroying organ function. There is overwhelming evidence that TGF-β is an important causative factor in these conditions, both from animal models of human disease and from humans with disease (reviewed in *Border and Noble*, supra). The results summarized in the Border review describe several *in vivo* animal models where the inhibition of

TGF-β by either anti-TGF-β antibodies or by decorin reduced or prevented fibrotic conditions caused by the deleterious accumulation of extracellular matrix.

Moreover, other *in vivo* results have been obtained which show that inhibiting TGF-β activity suppresses excessive extracellular matrix production and leads to normal tissue repair. These other *in vivo* results include, for example, reduced scarring of dermal wounds (*Shah et al.*, Lancet, 339:213-214 (1992)), reduced pulmonary fibrosis (*Giri et al.*, Thorax, 48:959-966 (1993)), reduced fibrous scar tissue and inflammation at the site of brain injury (*Logan and Berry*, J. Exp. Med., 177:225-230 (1993)). Thus, it is respectfully submitted that those skilled in the art would reasonably expect that the use of anti-TGF-β antibody in the claimed methods would be useful in a variety pathologic conditions to decrease the TGF-β-incuced deleterious accumulation of extracellular matrix.

With respect to the Examiner's concern related to the term ECM component, set forth in Paper No. 46, p. 4, second paragraph, it is respectfully submitted that this concern has been rendered moot by the amendment to claim 21, as suggested by the Examiner in Paper No. 46. The Examiner's suggestion of acceptable alternative claim language is acknowledged with appreciation. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

The rejections of claims 21 and 24 under 35 U.S.C. §103 as allegedly unpatentable over Conner et al., J. Clin. Invest., **83**:1661-1666 (1989), and of claims 22 and 23 over Conner et al.,

supra, iv view of McKay et al., J. Clin. Invest., **83**:1160-1167 (1989), is respectfully traversed. It is respectfully submitted that the Rule 131 Declaration, previously submitted on October 1, 1996, with Applicants' Response to Paper No. 42, provides sufficient evidence to antedate the Conner and McKay prior art references relied upon by the Examiner.

In order to antedate a prior art reference under Rule 131, Applicants must show conception of the claimed subject matter prior to the prior art date in question, coupled with a diligent reduction to practice. It is respectfully submitted that prior to April 1989, Applicants did in fact conceive methods of using anti-TGF-β to decrease deleterious accumulation of ECM in vivo, as oppposed to the mere conception and reduction to practice of in vitro methods. As recognized the CAFC, it is respectfully submitted that the in vitro experiments set forth in the Rule 131 Declaration are merely the prerequisite "first link in the screening chain" of ultimately reducing to practice the desired in vivo methods. For example, the CAFC in Cross v. Iizuka stated that:

> [w]e perceive no insurmountable difficulty ... in finding that the first link in the screening chain, in vitro testing, may establish a practical utility for the compound in question. Successful **in vitro testing will marshal resources and direct the expenditure of effort to further in vivo testing** of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an in vivo utility. (emphasis added)

Cross v. Iizuka, 753 F.2d 1040, 227 USPQ 739, 748 (Fed. Cir. 1985). Thus, the CAFC recognizes that initial in vitro screening assays are conducted for the purpose of determining which compounds are suitable for further in vivo testing. Because Applicants' in vitro screening assays were conducted for the purpose of determining whether the use of anti-TGF-β antibody was suitable for further in vivo testing, it is respectfully submitted that Applicants' in vitro screening conducted prior to April 1989 necessarily encompasses the conception of in vivo methods.

In addition, the Examiner acknowledges in Paper No. 34, p. 8, first paragraph, that:

> [I]t would have been obvious to one of ordinary skill to administer the antibodies in vivo in order to determine the therapeutic effect of the antibodies on disease progression. One of ordinary skill would have had a reasonable expectation of success in achieving retardation of the...disease by using the antibody to TGF-beta **since the use of antibodies to target specific cells in vivo is a technique old and well known in the art** and [Applicant] clearly shows the ability of the antibody to block the TGF-beta effect in vitro. (emphasis added)

Analgous to the Examiner's above-acknowledgment in Paper No. 34, it is respectfully submitted that Applicants' successful in vitro results using anti-TGF-β antibody encompasses the motivation, and therefore conception, to use such anti-TGF-β antibodies in vivo. Thus, the prior Rule 131 Declaration of the inventors clearly establishes conception of the claimed methods of using anti-

TGF-β, in vivo, in a tissue to decrease deleterious accumulation of ECM. It is respectfully submitted that Applicants diligently reduced to practice the claimed in vivo methods as evidence by the filing of the above-identified patent application. Therefore, it is respectfully submitted that the Conner and McKay references are not properly available as prior art against the pending claims. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

**CONCLUSION**

In view of the above amendments and remarks, reconsideration and favorable action on all pending claims is respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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Robert T. Ramos
Registration No. 37,915
Telephone: (619) 535-9001
Facsimile: (619) 535-8949

CAMPBELL & FLORES LLP
4370 La Jolla Village Drive, Suite 700
San Diego, California 92122